REMARKS

By this amendment, Applicants affirm the election of the invention of Group I. However, Applicants note that the invention is not drawn to methods of detecting a nucleic acid in a plant or an animal, a transgenic plant or animal having the nucleic acid or using said animal or plant. Instead, the present invention is drawn to methods and nucleic acid molecules for deleting said nucleic acid molecules in a specified manner in an organism. Furthermore, one of the utilities of this invention is that said nucleic acid molecules will be deleted from transgenic organisms when and if said organisms produce progeny.

Claims 1-17, 19-35 and 37 have been rejected by the Examiner. Claims 1-17, 19-35 and 37 were rejected under 35 U.S.C. 112, first paragraph for lack of enablement. Claims 11, 14, 22-24 and 27-34 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Claims 1, 20, 24 and 27-34 have been amended.

Claim Rejection – 35 U.S.C. §112, First Paragraph

The Office Action rejected claims 1-17, 19-35 and 37 under 35 U.S.C. §112, first paragraph, because the specification allegedly does not provide enablement for a method for deleting a nucleic acid sequence in a specified tissue of all organisms from a DNA introduced into the organism. Claim 1 has been amended to be directed to a method for deleting a nucleic acid from a DNA molecule that has been introduced into an organism, whereby said sequence is deleted in a tissue-specific manner.

The Examiner has noted that the specification is enabling for a method for deleting a nucleic acid sequence in a specified tissue of a mouse from a nucleic acid molecule introduce into the mouse. The Examiner is of the opinion, however, that the specification does not reasonably provide enablement for a method for deleting a nucleic acid sequence is a specified tissue of all organisms, **comprising introducing a DNA molecule**... " (*emphasis added).* The Examiner is of the opinion that an element essential to the claimed invention are "embryonic stem cells." Further, the Examiner notes that embryonic stem cell technology is limited to mouse cells. The Examiner has thus reasoned that since germline transmission of ES cells has not been demonstrated in other than mouse cells, only germline mouse cells are enabled by the

specification. Applicants respectfully submit that embryonic stem cells are not an essential element of the invention of the claims as amended.

At page 7, the Examiner has addressed applicants claims that are directed to the use of the above construct in germline gene therapy and noted that since germline gene therapy protocols are inefficient and too preliminary, the claims are not enabled. The Examiner goes on to note at page 8 that since the specification contains no working examples which show therapeutic gene expression *in vivo,* the claims are not enabled. Once again, the Applicants note that gene therapy is not an element of the claims, especially in light of the present amendments thereto.

With regard to stem cells, these cells are cited in the specification as an example of how the invention works in one particular cell type. To wit, when a gene has inserted into an embryonic stem cell, the methods of the present invention can be utilized to excise the gene, as demonstrated by the examples in the specification. As noted at page 6 and Table 1, male chimeric mice having a copy of a DNA molecule of the invention excised a targeted gene from the germline, thus preventing transmission of the gene to progeny. The invention is also not directed to gene therapy. The claims are directed to methods and molecules for excising a nucleic acid sequence from a DNA molecule that has been introduced into an organism. As noted at page 2, lines 3-4 of the Specification, the present invention is directed to a method wherein nucleic acid sequences are deleted in a tissue specific manner. In alternative embodiments, the method provides for deletion of nucleic acids in germline or somatic tissue. Simply by providing a method whereby the regulation of when and where a DNA fragment is maintained in a cellular chromosomal complement, the claimed invention does not require therapeutic expression of a gene. In fact, in some embodiments the method of the invention will prevent therapeutic expression of a heterologous gene when, for example, the method is utilized to prevent transmission of said heterologous gene to progeny of a transgenic animal. Thus, the invention is not directed to generation of a transgenic animal, but instead is directed, *inter alia*, to the prevention of a transgenic animal producing progeny containing a heterologous DNA. In sum, the methods and molecules of the present invention do not require therapeutic expression of any gene. Instead, all that is required is expression of a regulatory gene fragment which prevents unwanted transmission or persistence of the fragment.

The present invention provides a method wherein a nucleic acid sequence can be excised in a tissue-specific manner from any DNA molecule. For example, at page 5, lines 12-22, it is noted that the invention has been illustrated with reference to male germline of animals (specifically mice) and using the *Cre* gene. As noted, however, the method is also applicable to somatic tissue and female germline of animals. Furthermore, recombinase systems other than *Cre* can be utilized. The example in the specification merely provides one way in which the method of deleting DNA in a tissue specific manner can be practiced. The specification goes on to explain, however, that the methods and molecules recited in the claims will have a wide range of applicability, with stem cells being only one part of that range. The applicants thus submit that the specification is enabling for what is claimed, *i.e.,* a method for deleting specific nucleic acids sequences in a tissue specific fashion.

In view of the amendments to the claims and above arguments, it is requested that the rejection under 35 U.S.C. 112, first paragraph for lack of enablement be withdrawn.

Claim Rejection – 35 U.S.C. §112, Second Paragraph

The Office Action rejected claims 11, 14, 22-24 and 27-34 under 35 U.S.C. second paragraph, for being indefinite. Claims 20, 24 and 27-34 have been amended. It is submitted that the amendments overcome this ground of rejection. With regard to claims 11 and 14, the Office Action rejected these claims for lack of antecedent basis for "the introduction" of the DNA molecule into an organism. Claim 11 depends from claim 7, which depends from claim 1. Claim 14 depends from claim 8, which also depends from claim 7. Claim 1 recites a method which comprises, *inter alia*, "...introducing a DNA into an organism..." It is submitted that the language of claim 1 reciting "introducing a DNA" provides sufficient antecedent basis for the subsequent claims which further clarify the effect of "...the introduction of the DNA..."

In view of the above arguments, it is requested that the rejection under 35 U.S.C. 112, first paragraph for lacking a written description be withdrawn.

CONCLUSION

In view of the above amendments and remarks, it is believed that the present application satisfies the provisions of the patent statutes and is patentable over the cited prior art. Reconsideration of this application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned if it will help expedite the allowance of the application.

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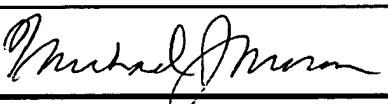
SIGNATURE			DATE	12/20/01	
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Attachments: Version with markings to show changes made

Substitute Paragraph, Page 2, First Full Paragraph : V rsion with markings to show changes made

The present invention is directed to a method for deleting nucleic acid sequences in a tissue specific manner. In one embodiment, nucleic acid sequences are specifically deleted in germline tissue. In a second embodiment, nucleic acid sequences are specifically deleted in desired somatic tissue. The present invention is further directed to a ~~DNBA~~ DNA molecule for use in the method.

Amended Claims : Version with markings to show changes made

1.(Amended) A method for deleting a nucleic acid sequence ~~in a specified tissue of an organism~~ from a DNA molecule that has been introduced into ~~the~~ an organism, whereby the sequence is deleted in a tissue-specific manner ~~which comprises:~~
~~(a) introducing a DNA molecule into an organism~~, said DNA molecule ~~comprises~~ comprising a recombinase site, a tissue-specific promoter, a recombinase gene, a foreign DNA and a recombinase site~~; and~~
~~(b)~~ , the method comprising growing said organism such that the tissue-specific promoter is active, ~~for expression of~~ said recombinase gene is expressed in the specified tissue, ~~whereby~~ and said foreign DNA is deleted ~~in the specified tissue during growth of the organism~~.

20. (Amended) A nucleic acid molecule comprising (a) a recombinase site, (b) a tissue-specific promoter, (c) a recombinase ~~coding sequence~~ gene, (d) a foreign DNA and (e) a recombinase site.

24. (Amended) The ~~method~~ molecule of claim 20, wherein said molecule further comprises a gene which is desired to be expressed in an organism.

27. (Amended)The ~~method~~ molecule of claim 25, wherein said molecule further comprises a gene which is desired to be expressed in an organism.

28. (Amended)The ~~method~~ molecule of claim 26, wherein said molecule further comprises a gene which is desired to be expressed in an organism.

29. (Amended) The ~~method~~ molecule of claim 20, wherein said foreign DNA is heterologous DNA.

30. (Amended) The ~~method~~ molecule of claim 25, wherein said foreign DNA is heterologous DNA.

31. (Amended) The ~~method~~ molecule of claim 26, wherein said foreign DNA is heterologous DNA.

32. (Amended) The ~~method~~ molecule of claim 20, wherein said foreign DNA is a wild-type allele or fragment thereof of a gene for use in gene therapy.

33. (Amended) The ~~method~~ molecule of claim 25, wherein said foreign DNA is a wild-type allele or fragment thereof of a gene for use in gene therapy.

34. (Amended) The ~~method~~ molecule of claim 26, wherein said foreign DNA is a wild-type allele or fragment thereof of a gene for use in gene therapy.